Activity Report 2018

Project-Team MAMBA

Modelling and Analysis for Medical and Biological Applications

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Project-Team MAMBA

Creation of the Team: 2014 January 01, updated into Project-Team: 2015 April 01

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1. Team, Visitors, External Collaborators

Research Scientists
Marie Doumic [Team leader, Inria, Senior Researcher, HDR]
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Diane Peurichard [Inria, Researcher]
Nastassia Pouradier Duteil [Inria, Researcher, from Sep 2018]
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Martin Strugarek [Ecole Nationale des Ponts et Chaussées, until Aug 2018]
Wen Sun [Inria, until Sep 2018]
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Lois Naudin [Inria, from Mar 2018 until Sep 2018]

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Jieling Zhao [IfADO, Dortmund, Germany]

2. Overall Objectives

2.1. Context and overall objectives of the project-team

The MAMBA (Modelling and Analysis in Medical and Biological Applications) team is the continuation of the BANG (Biophysics, Numerical Analysis and Geophysics) team, which itself was a continuation of the former project-team M3N. Historically, the BANG team, headed by Benoît Perthame during 11 years (2003-2013), has developed models, simulations and numerical algorithms for problems involving dynamics of Partial Differential Equations (PDEs).

The dynamics of complex physical or biophysical phenomena involves many agents, e.g. proteins or cells - which can be seen as active agents. Mathematically, they can be represented either explicitly as individuals with their dynamics modelled e.g. through branching trees and piecewise deterministic Markov processes (PDMP), or stochastic differential equations, or under certain conditions be grouped or locally averaged, in which case their dynamics is mimicked by Ordinary or Partial Differential Equations (ODEs/PDEs).

Biology and medicine presently face the difficulty to make sense of the data newly available by means of recent signal acquisition methods and to take appropriate actions through possible treatment pathways. Modeling through agent-based or continuous models is a unique way to explain (model) the observations and then compute, control and predict the consequences of the mechanisms under study. These are the overall goals of Mamba.

3. Research Program

3.1. Introduction

Data and image analysis, statistical, ODEs, PDEs, and agent-based approaches are used either individually or in combination, with a strong focus on PDE analysis and agent-based approaches. Mamba was created in January 2014 as a continuation of the BANG project-team, that had been headed by Benoît Perthame from 2003-2013, and in the last years increasingly broadened its subjects as its members developed their own research agendas. It aims at developing models, simulations, numerical and control algorithms to solve questions from life sciences involving dynamics of phenomena encountered in biological systems such as protein intracellular spatio-temporal dynamics, cell motion, early embryonic development, multicellular growth, wound healing and liver regeneration, cancer evolution, healthy and tumor growth control by pharmaceuticals, protein polymerization occurring in neurodegenerative disorders, control of dengue epidemics, etc.

Another guideline of our project is to remain close to the most recent questions of experimental biology or medicine, to design models and problems under study as well as the related experiments to be carried out by our collaborators in biology or medicine. In this context, our ongoing collaborations with biologists and physicians: the collaboration with St Antoine Hospital in Paris within the Institut Universitaire de Cancérologie of Sorbonne Université (IUC, Luis Almeida, Jean Clairambault, Dirk Drasdo, Alexander Lorz, Benoît Perthame); Institut Jacques Monod (Luis Almeida); the INRA team headed by Human Rezaei and Wei-Feng Xue's team in the university of Canterbury through the ERC Starting Grant SKIPPER^{AD} (Marie Doumic); our collaborators within the HTE program (François Delhommeau at St Antoine, Thierry Jaffredo, and Delphine Salort at IBPS, Sorbonne Université, Paris; François Vallette at INSERM Nantes); Frédéric

Thomas at CREEC, Montpellier; Hôpital Paul Brousse through ANR-IFlow and ANR-iLite; and the close experimental collaborations that emerged through the former associate team QUANTISS (Dirk Drasdo), particularly at the Leibniz Institute for Working Environment and Human Factors in Dortmund, Germany; or more recently with Yves Dumont at CIRAD, Montpellier, are key points in our project.

Our main objective is the creation, investigation and transfer of new models, methods (for analysis but also for control) and algorithms. In selected cases software development as that of CellSys and TiQuant by D. Drasdo and S. Hoehme is performed. More frequently, the team develops "proof of concept" numerical codes in order to test the adequacy of our models to experimental biology.

Taking advantage of the last 4-year evaluation of MAMBA (September 2017), we have reorganized the presentation of our research program in three main methodological axes. Two main application axes are presented in the next Section. Evolving along their own logic in close interaction with the methodological axes, they are considered as application-driven research axes in themselves. The methodological research axes are the following.

Axis 1 is devoted to work in physiologically-based design, analysis and control of population dynamics. It encompasses populations of bacteria, of cancer cells, of neurons, of aggregating proteins, etc. whose dynamics are represented by partial differential equations (PDEs), structured in evolving physiological traits, such as cell age, cell size, time elapsed since last firing (neurons).

Axis 2 is devoted to reaction equations and motion equations of agents in living systems. It aims at describing biological phenomena such as tumor growth, chemotaxis and wound healing.

Axis 3 tackles the question of model and parameter identification, combining stochastic and deterministic approaches and inverse problem methods in nonlocal and multi-scale models.

3.2. Methodological axis 1: analysis and control for population dynamics

Personnel

Pierre-Alexandre Bliman, Jean Clairambault, Marie Doumic, Benoît Perthame, Nastassia Pouradier Duteil, Philippe Robert

Project-team positioning

Population dynamics is a field with varied and wide applications, many of them being in the core of MAMBA interests - cancer, bacterial growth, protein aggregation. Their theoretical study also brings a qualitative understanding on the interplay between individual growth, propagation and reproduction in such populations. In the previous periods of evaluation, many results where obtained in the BANG team on the asymptotic and qualitative behavior of such structured population equations, see e.g. [126], [73], [94], [84]. Other Inria teams interested by this domain are Mycenae, Numed and Dracula, with which we are in close contacts. Among the leaders of the domain abroad, we can cite among others our colleagues Tom Banks (USA), Graeme Wake (New Zealand), Glenn Webb (USA), Jacek Banasiak (South Africa), Odo Diekmann (Netherlands), with whom we are also in regular contact. Most remarkably and recently, connections have also been made with probabilists working on Piecewise Deterministic Markov Processes (F. Malrieu at the university of Rennes, Jean Bertoin at the ETH in Zurich, Vincent Bansaye at Ecole Polytechnique, Julien Berestycki at Cambridge, Amaury Lambert at College de France, M. Hoffmann at Paris Dauphine), leading to a better understanding of the links between both types of results – see also the Methodological axis 3.

Scientific achievements

We divide this research axis, which relies on the study of structured population equations, according to four different applications, bringing their own mathematical questions, e.g., stability, control, or blow-up.

Time asymptotics for nucleation, growth and division equations

Following the many results obtained in the BANG team on the asymptotic and qualitative behavior of structured population equation, we put our effort on the investigation of limit cases, where the trend to a steady state or to a steady exponential growth described by the first eigenvector fails to happen. In [78], the case of equal mitosis (division into two equally-sized offspring) with linear growth rate was studied, and strangely enough, it appeared that the general relative entropy method could also be adapted to such a non-dissipative case. Many discussions and common workshops with probabilists, especially through the ANR project PIECE coordinated by F. Malrieu, have led both communities to work closer.

In [92], the case of constant fragmentation rate and linear growth rate has been investigated in a deterministic approach, whereas similar questions were simultaneously raised but in a stochastic process approach in [75].

We also enriched the models by taking into account a nucleation term, modeling the spontaneous formation of large polymers out of monomers [137]. We investigated the interplay between four processes: nucleation, polymerization, depolymerization and fragmentation.

The ERC Starting Grant SKIPPER^{AD} (Doumic) supported and was the guideline for the study of nucleation, growth and fragmentation equations.

Cell population dynamics and its control
One of the important incentives for such model design, source of many theoretical works, is the challenging question of drug-induced drug resistance in cancer cell populations, described in more detail below in the Applicative axis 1, Cancer. The adaptive dynamics setting used consists of phenotype-structured integro-differential [or reaction-diffusion, when phenotype instability is added under the form of a Laplacian] equations describing the dynamic behavior of different cell populations interacting in a Lotka-Volterra-like manner that represents common growth limitation due to scarcity of expansion space and nutrients. The phenotype structure allows us to analyse the evolution in phenotypic traits of the populations under study and its asymptotics for two populations [119], [116], [115], [117]. Space may be added as a complementary structure variable provided that something is known of the (Cartesian) geometry of the population [118], which is seldom the case.

Modelling, observation and identification of the spread of infectious diseases
Epidemiological models are made to understand and predict the dynamics of the spread of infectious diseases. We initiated studies with the aim to understand how to use epidemiological data (typically given through incidence rate) in order to estimate the state of the population as well as constants, characteristic of the epidemics such as the transmission rate. The methods rely on observation and identification techniques borrowed from control theory.

Modelling Mendelian and non-Mendelian inheritances in density-dependent population dynamics
Classical strategies for controlling mosquitoes responsible of vector-borne disease are based on mechanical methods, such as elimination of oviposition sites; and chemical methods, such as insecticide spraying. Long term usage of the latter generates resistance [81], [103], transmitted to progeny according to Mendelian inheritance (in which each parent contributes randomly one of two possible alleles for a trait). New control strategies involve biological methods such as genetic control, which may either reduces mosquito population in a specific area or decreases the mosquito vector competence [61], [112], [144]. Among the latter, infection of wild populations by the bacterium *Wolbachia* appears promising (see also Applicative axis 2 below). Being maternally-transmitted, the latter obeys non-Mendelian inheritance law. Motivated by the effects of the (possibly unwanted) interaction of these two types of treatment, we initiated the study of modelling of Mendelian and non-Mendelian inheritances in density-dependent population dynamics.

Control of collective dynamics

The term *self-organization* is used to describe the emergence of complex organizational patterns from simple interaction rules in collective dynamics systems. Such systems are valuable tools to model various biological systems or opinion dynamics, whether it be the collective movement of animal groups, the organization of cells in an organism or the evolution of opinions in a large crowd. A special case of self-organization is given by *consensus*, i.e. the situation in which all agents' state variables converge. Another phenomenon is that of *clustering*, when the group is split into clusters that each converge to a different state. We have designed optimal control strategies to drive collective dynamics to consensus. In the case where consensus and clustering are situations to be avoided (for example in crowd dynamics), we designed control strategies to keep the system away from clustering.

Models of neural network

Mean field limits have been proposed by biophysicists in order to describe neural networks based on physiological models. The various resulting equations are called integrate-and-fire, time elapsed models, voltage-conductance models. Their specific nonlinearities and the blow-up phenomena make their originality which has led to develop specific mathematical analysis [129], followed by [124], [111], [130], [83]. This field also yields a beautiful illustration for the capacity of the team to combine and compare stochastic and PDE modelling (see Methodological axis 3), in [87].

Models of interacting particle systems

The organisation of biological tissues during development is accompanied by the formation of sharp borders between distinct cell populations. The maintenance of this cell segregation is key in adult tissue homeostatis, and its disruption can lead tumor cells to spread and form metastasis. This segregation is challenged during tissue growth and morphogenesis due to the high mobility of many cells that can lead to intermingling. Therefore, understanding the mechanisms involved in the generation and maintain of cell segregation is of tremendous importance in tissue morphogenesis, homeostasis, and in the development of various invasive diseases such as tumors. In this research axis, we aim to provide a mathematical framework which enables to quantitatively link the segregation and border sharpening ability of the tissue to these cell-cell interaction phenomena of interest [72]. As agent-based models do not enable precise mathematical analysis of their solutions due to the lack of theoretical results, we turn towards continuous -macroscopic- models and aim to provide a rigorous link between the different models [71].

Collaborations

- Nucleation, growth and fragmentation equations: **Juan Calvo**, university of Granada, came for two one-month visits, **Miguel Escobedo**, University of Bilbao (see also Methodological axis 3), **Pierre Gabriel**, University of Versailles-Saint Quentin, former B. Perthame and M. Doumic's Ph.D student, who now co-supervises Hugo Martin's Ph.D thesis. **Piotr Gwiązda**, Polish Academy of Sciences, Poland, **Emil Wiedemann**, University of Bonn, Germany, **Klemens Fellner**, university of Graz, Austria.

- Cell population dynamics and its control: **Tommaso Lorenzi**, former Mamba postdoc, now at the University of St. Andrews, Scotland, maintains a vivid collaboration with the Mamba team. He is in particular an external member of the HTE program MoGlImaging (see also Applicative axis 1). **Emmanuel Trélat**, Sorbonne Université professor, member of LJLL and of the CAGE Inria team, is the closest Mamba collaborator for optimal control. **Benedetto Piccoli**, Professor at Rutgers University (Camden, New Jersey), is collaborating on the analysis and control of collective dynamics.

- Mendelian inheritance and resistance in density-dependent population dynamics: **Pastor Pérez-Estigarribia, Christian Schaerer**, Universidad Nacional de Asunción, Paraguay.

- Neural networks: **Delphine Salort,** Professor Sorbonne Université, Laboratory for computations and quantification in biology, and **Patricia Reynaud**, University of Nice, **Maria Cáceres**, University of Granada.

- Models of interacting particle systems: **Pierre Degond**, Imperial College London, **MAPMO, Orléans**, **Ewelina Zatorska**, University College London, **Anais Khuong**, Francis Crick Institute

3.3. Methodological axis 2: reaction and motion equations for living systems

Personnel

Luis Almeida, Benoît Perthame, Diane Peurichard, Nastassia Pouradier Duteil.

Project-team positioning

The Mamba team had initiated and is a leader on the works developed in this research axis. It is a part of a consortium of several mathematicians in France through the ANR Blanc project *Kibord*, which involves in particular members from others Inria team (DRACULA, REO). Finally, we mention that from Sept. 2017 on, Mamba benefited from the ERC Advanced Grant ADORA (Asymptotic approach to spatial and dynamical organizations) of Benoît Perthame.

Scientific achievements

We divide this research axis, which relies on the study of partial differential equations for space and time organisation of biological populations, according to various applications using the same type of mathematical formalisms and methodologies: asymptotic analysis, weak solutions, numerical algorithms.

Aggregation equation

In the mathematical study of collective behavior, an important class of models is given by the aggregation equation. In the presence of a non-smooth interaction potential, solutions of such systems may blow up in finite time. To overcome this difficulty, we have defined weak measure-valued solutions in the sense of duality and its equivalence with gradient flows and entropy solutions in one dimension [109]. The extension to higher dimensions has been studied in [86]. An interesting consequence of this approach is the possibility to use the traditional finite volume approach to design numerical schemes able to capture the good behavior of such weak measure-valued solutions [102], [108].

Identification of the mechanisms of single cell motion.

In this research axis, we aim to study the mechanisms of single cell adhesion-based and adhesion free motion. This work is done in the frame of the recently created associated team MaMoCeMa (see Section 9) with the WPI, Vienna. In a first direction [140] with N. Sfakianakis (Heidelberg University), we extended the live-cell motility Filament Based Lamellipodium Model to incorporate the forces exerted on the lamellipodium of the cells due to cell-cell collision and cadherin induced cell-cell adhesion. We took into account the nature of these forces via physical and biological constraints and modelling assumptions. We investigated the effect these new components had in the migration and morphology of the cells through particular experiments. We exhibit moreover the similarities between our simulated cells and HeLa cancer cells.

In a second work done in collaboration with the group of biologist at IST (led by **Michael Sixt** Austria), we developed and analyzed a two-dimensional mathematical model for cells migrating without adhesion capabilities [110]. Cells are represented by their cortex, which is modelled as an elastic curve, subject to an internal pressure force. Net polymerization or depolymerization in the cortex is modelled via local addition or removal of material, driving a cortical flow. The model takes the form of a fully nonlinear degenerate parabolic system. An existence analysis is carried out by adapting ideas from the theory of gradient flows. Numerical simulations show that these simple rules can account for the behavior observed in experiments, suggesting a possible mechanical mechanism for adhesion-independent motility.

Free boundary problems for tumor growth.

Fluid dynamic equations are now commonly used to describe tumor growth with two main classes of models: those which describe tumor growth through the dynamics of the density of tumoral cells subjected to a mechanical stress; those describing the tumor through the dynamics of its geometrical domain thanks to a Hele-Shaw-type free boundary model. The first link between these two classes of models has been rigorously obtained thanks to an incompressible limit in [128] for a simple model. This result has motivated the use of another strategy based on viscosity solutions, leading to similar results, in [113].

Since more realistic systems are used in the analysis of medical images, we have extended these studies to include active motion of cells in [127], viscosity in [132] and proved regularity results in [120]. The limiting Hele-Shaw free boundary model has been used to describe mathematically the invasion capacity of a tumour by looking for travelling wave solutions, in [131], see also Methodological axis 3. It is a fundamental but difficult issue to explain rigorously the emergence of instabilities in the direction transversal to the wave propagation. For a simplified model, a complete explanation is obtained in [114].

Two-way coupling of diffusion and growth.
We are currently developing a mathematical framework for diffusion equations on time-evolving manifolds, where the evolution of the manifold is a function of the distribution of the diffusing quantity. The need for such a framework takes it roots in developmental biology. Indeed, the growth of an organism is triggered by signaling molecules called morphogens that diffuse in the organism during its development. Meanwhile, the diffusion of the morphogens is itself affected by the changes in shape and size of the organism. In other words, there is a complete coupling between the diffusion of the morphogens and the evolution of the shapes. In addition to the elaboration of this theoretical framework, we also collaborate with a team of developmental biologists from Rutgers University (Camden, New Jersey) to develop a model for the diffusion of Gurken during the oogenesis of *Drosophila*.

Collaborations

- Shanghai Jiao Tong University, joint publications with Min Tang on bacterial models for chemotaxis and free boundary problems for tumor growth.
- Imperial College London, joint works with José Antonio Carrillo on aggregation equation.
- University of Maryland at College Park, UCLA, Univ. of Chicago, Univ. Autónoma de Madrid, Univ. of St. Andrews (Scotland), joint works on mathematics of tumor growth models.
- Joint work with Francesco Rossi (Università di Padova, Italy) and Benedetto Piccoli (Rutgers University, Camden, New Jersey, USA) on Developmental PDEs.
- Cooperation with Shugo Yasuda (University of Hyogo, Kobe, Japan) and Vincent Calvez (EPI Dracula) on the subject of bacterial motion.
- Cooperation with Nathalie Ferrand (INSERM), Michèle Sabbah (INSERM) and Guillaume Vidal (Centre de Recherche Paul Pascal, Bordeaux) on cell aggregation by chemotaxis.
- Nicolas Vauchelet, Université Paris 13

3.4. Methodological axis 3: Model and parameter identification combining stochastic and deterministic approaches in nonlocal and multi-scale models

Personnel

Marie Doumic, Dirk Drasdo.

Project-team positioning

Mamba developed and addressed model and parameter identification methods and strategies in a number of mathematical and computational model applications including growth and fragmentation processes emerging in bacterial growth and protein misfolding, in liver regeneration [97], TRAIL treatment of HeLa cells [74], growth of multicellular spheroids [107], blood detoxification after drug-induced liver damage [139], [101].

This naturally led to increasingly combine methods from various fields: image analysis, statistics, probability, numerical analysis, PDEs, ODEs, agent-based modeling methods, involving inverse methods as well as direct model and model parameter identification in biological and biomedical applications. Model types comprise agent-based simulations for which Mamba is among the leading international groups, and Pharmocokinetic (PK) simulations that have recently combined in integrated models (PhD theses Géraldine Cellière, Noémie Boissier). The challenges related with the methodological variability has led to very fruitful collaborations with internationally renowned specialists of these fields, e.g. for bacterial growth and protein misfolding with Marc Hoffmann (Paris Dauphine) and Patricia Reynaud-Bouret (University of Nice) in statistics, with Tom Banks (Raleigh, USA) and Philippe Moireau (Inria M3DISIM) in inverse problems and data assimilation, and with numerous experimentalists.

Scientific achievements

Direct parameter identification is a great challenge particularly in living systems in which part of parameters at a certain level are under control of processes at smaller scales.

Estimation methods for growing and dividing populations
In this domain, all originated in two papers in collaboration with J.P. Zubelli in 2007 [133], [96], whose central idea was to used the asymptotic steady distribution of the individuals to estimate the division rate. A series of papers improved and extended these first results while keeping the deterministic viewpoint, lastly [78]. The last developments now tackle the still more involved problem of estimating not only the division rate but also the fragmentation kernel (i.e., how the sizes of the offspring are related to the size of the dividing individual) [13]. In parallel, in a long-run collaboration with statisticians, we studied the Piecewise Deterministic Markov Process (PDMP) underlying the equation, and estimated the division rate directly on sample observations of the process, thus making a bridge between the PDE and the PDMP approach in [95], a work which inspired also very recently other groups in statistics and probability [75], [105] and was the basis for Adélaïde Olivier's Ph.D thesis [122], [106] and of some of her more recent works [123] (see also axis 5).

Data assimilation and stochastic modeling for protein aggregation

Estimating reaction rates and size distributions of protein polymers is an important step for understanding the mechanisms of protein misfolding and aggregation (see also axis 5). In [63], we settled a framework problem when the experimental measurements consist in the time-dynamics of a moment of the population.

To model the intrinsic variability among experimental curves in aggregation kinetics - an important and poorly understood phenomenon - Sarah Eugène's Ph.D, co-supervised by P. Robert [99], was devoted to the stochastic modeling and analysis of protein aggregation, compared both with the deterministic approach traditionally developed in Mamba [137] and with experiments.

Statistical methods decide on subsequently validated mechanism of ammonia detoxification

To identify the mechanisms involved in ammonia detoxification [101], 8 candidate models representing the combination of three possible mechanisms were developed (axis 5). First, the ability of each model to capture the experimental data was assessed by statistically testing the null hypothesis that the data have been generated by the model, leading to exclusion of one of the 8 models. The 7 remaining models were compared among each other by the likelihood ratio. The by far best models were those containing a particular ammonia sink mechanism, later validated experimentally (axis 5). For each of the statistical tests, the corresponding test statistics has been calculated empirically and turned out to be not chi2-distributed in opposition to the usual assumption stressing the importance of calculating the empirical distribution, especially when some parameters are unidentifiable. This year the ammonia detoxification mechanisms have been integrated in a spatial-temporal agent-based model of a liver lobule (the smallest repetitive anatomical unit of liver) and studied for normal and fibrotic liver.

Collaborations

- **Marc Hoffmann,** Université Paris-Dauphine, for the statistical approach to growth and division processes [95], **M. Escobedo**, Bilbao and **M. Tournus**, Marseille, for the deterministic approach.

- **Tom Banks**, North Carolina State University, and **Philippe Moireau,** Inria M3DISIM, for the inverse problem and data assimilation aspects [70], [62]
- **Jan G. Hengstler**, IfADo, Dortmund, Germany

4. Application Domains

4.1. Introduction

The team has two main application-driven research axes.

Applicative axis 1 focuses on cancer, an application on which almost all team members work, with various approaches. A main focus of the team is to study cancer as a Darwinian evolutionary phenomenon in phenotype-structured cell populations. Optimal control methods take into account the two main pitfalls of clinical cancer therapeutics, namely unwanted toxic side effects in healthy cell populations and drug resistance in cancer cell populations. Other studies concern telomere shortening, and multi-scale models.

Applicative axis 2 is devoted to growth, evolution and regeneration in populations and tissues. It involves protein aggregation and fragmentation models for neurodegenerative diseases (prion, Alzheimer), organ modeling, mainly of the liver, its damages induced by toxic molecules, and its regeneration after toxic insult. Newcomers in this applicative field are epidemiological modeling of propagation of insect vector-borne diseases by reaction-diffusion equations and of their optimal control, bacterial growth and wound healing.

4.2. Applicative axis 1: Focus on cancer

Personnel

Luis Almeida, Cécile Carrère, Jean Clairambault, Marie Doumic, Dirk Drasdo, Benoît Perthame, Diane Peurichard.

Project-team positioning

The MAMBA team designs and analyses mathematical models of tumor growth and therapy, at the cell population level, using agent-based or partial differential equations, with special interest in methodologies for therapeutic optimisation using combined anticancer drug treatments. Rather than, or not only, modeling the effect of drugs on molecular targets, we represent these effects by their *functional* consequences on the fate of healthy and cancer cell populations: proliferation (velocity of the cell division cycle, decreasing it, e.g., by antagonizing growth factor receptors), apoptosis, cell death or senescence.

Our goal in doing this is to circumvent the two main issues of anticancer therapy in the clinic, namely unwanted toxic side effects in populations of healthy cells and emergence of drug-induced drug resistance in cancer cell populations. This point of view leads us to take into account phenomena of transient and reversible resistance, observed in many cancer cell populations, by designing and analyzing models of cell populations structured in continuous phenotypes, relevant for the description of the behavior of cell populations exposed to drugs: either degree of resistance to a given drug, or potential of resistance to drug-induced stress, proliferation potential, and plasticity.

Such modeling options naturally lead us to to take into account in a continuous way (i.e., by continuous-valued phenotype or relevant gene expression) the wide phenotypic heterogeneity of cancer cell populations. They also lead us to adopt the point of view of *adaptive dynamics* according to which characteristic traits of cell populations evolve with tumor environmental pressure (drugs, cytokines or metabolic conditions, mechanical stress and spatial conditions), in particular from drug sensitivity to resistance. This position is original on the international scene of teams dealing with drug resistance in cancer.

Scientific achievements

Modeling Acute Myeloid Leukemia (AML) and its control by anticancer drugs by PDEs and Delay Differential equations

In collaboration with Catherine Bonnet (Inria DISCO, Saclay) and François Delhommeau (St Antoine hospital in Paris), together with DISCO PhD students José Luis Avila Alonso and Walid Djema, this theme has led to common published proceedings of conferences: IFAC, ACC, CDC, MTNS [66], [67], [68], [77], [91], [65]. These works study the stability of the haematopoietic system and its possible restabilization by combinations of anticancer drugs with functional targets on cell populations: proliferation, apoptosis, differentiation.

Adaptive dynamics setting to model and circumvent evolution towards drug resistance in cancer by optimal control
We tackle the problem to represent and inhibit - using optimal control algorithms, in collaboration with Emmanuel Trélat, proposed Inria team CAGE - drug-induced drug resistance in cancer cell populations. This theme, presently at the core of our works on cancer modeling with a evolutionary perspective on tumor heterogeneity, is documented in a series of articles [88], [89], [115], [116], [118]. Taking into account the two main pitfalls of cancer therapy, unwanted side effects on healthy cells and evolution towards resistance in cancer cells, it has attracted to our team the interest of several teams of biologists, with whom we have undertaken common collaborative works, funded by laureate answers to national calls (see ITMO Cancer HTE call).

This theme is also at the origin of methodological developments (see Research axis 1). In collaboration with Shensi Shen from Institut Gustave Roussy and Francois Vallette from Université de Nantes, we aim to develop simple non-spatial models to understand the mechanisms of drug resistance acquisition -and lost- in melanoma and glioblastoma. The models are systematically compared with in vitro and in vivo data generated by our collaborators and treated via image processing techniques developed in the team.

Senescence modeling by telomere shortening
In many animals, aging tissues accumulate senescent cells, a process which is beneficial to protect from cancer in the young organism. In collaboration with Teresa Teixeira and Zhou Xu from IBCP, we proposed a mathematical model based on the molecular mechanisms of telomere replication and shortening and fitted it on individual lineages of senescent Saccharomyces cerevisiae cells, in order to decipher the causes of heterogeneity in replicative senescence [79].

Biomechanically mediated growth control of cancer cells

Model simulations indicate that the response of growing cell populations on mechanical stress follows a simple universal functional relationship and is predictable over different cell lines and growth conditions despite the response curves look largely different. We developed a hybrid model strategy in which cells were represented by coarse-grained individual units calibrated in a high resolution cell model and parameterized each model cell by measurable biophysical and cell-biological parameters. Cell cycle progression in our model is controlled by volumetric strain, the latter being derived from a bio-mechanical relation between applied pressure and cell compressibility. After parameter calibration from experiments with mouse colon carcinoma cells growing against the resistance of an elastic alginate capsule, the model adequately predicts the growth curve in i) soft and rigid capsules, ii) in different experimental conditions where the mechanical stress is generated by osmosis via a high molecular weight dextran solution, and iii) for other cell types with different growth kinetics. Our model simulation results suggest that the growth response of cell population upon externally applied mechanical stress is the same, as it can be quantitatively predicted using the same growth progression function [44].

Collaborations

- AML modelling: **Catherine Bonnet**, DISCO Inria team, Saclay, and **François Delhommeau**, INSERM St Antoine (also collaborator in the INSERM HTE laureate project EcoAML, see below).

- INSERM HTE laureate project MoGlImaging, headed by E. Moyal (Toulouse): **François Vallette**, CRCNA and INSERM Nantes

- INSERM HTE laureate project EcoAML, headed by **François Delhommeau**, INSERM St Antoine: François Delhommeau, Thierry Jaffredo (IBPS), Delphine Salort (LCQB-IBPS)

- Adaptive dynamics to model drug resistance and optimal control to circumvent it:

Alexandre Escargueil, Michèle Sabbah (1 PhD thesis in common), St Antoine Hospital, Paris

Emmanuel Trélat (1 PhD thesis in common) at Inria team CAGE and Laboratoire Jacques-Louis Lions at Sorbonne Université.

Frédéric Thomas at CREEC, Montpellier.

Tommaso Lorenzi (Univ. of St Andrews).

- Telomere shortening: **Teresa Teixeira** and **Zhou Xu** (IBCP, Paris), **Philippe Robert** (Inria RAP).
- TRAIL treatment: **Gregory Batt,** Inria Saclay and Inst. Pasteur (France)
- Biomechanical control of cancer cells: **Pierre Nassoy**, Bioimaging and Optofluidics Group, LP2N – UMR 5298. IOGS, CNRS & University of Bordeaux

4.3. Applicative axis 2: Growth, evolution and regeneration in populations and tissues

Personnel

Luis Almeida, Pierre-Alexandre Bliman, Marie Doumic, Dirk Drasdo, Benoît Perthame, Diane Peurichard, Nastassia Pouradier Duteil, Philippe Robert

Project-team positioning

The applications in this category span very different subjects from amyloid diseases, dengue fever, wound healing, liver regeneration and toxicity, up to bacterial growth and development of organisms. As the applications, the methods span a wide range. Those concerning identification of models and parameters with regard to data have partially been outlined in axis 3. Focus in this axis is on the model contribution to the biologically and/or medically relevant insights and aspects.
Liver-related modeling is partially performed within the Inria team MIMESIS (Strasbourg) with the focus on real-time, patient-specific biomechanical liver models to guide surgery and surgeons. Internationally, spatial temporal liver related models are developed in Fraunhofer MEVIS (Bremen), by T. Ricken (University of Stuttgart), and P. Segers group (Leuven). Different from these, Mamba has a strong focus on spatial-temporal modeling on the histological scale, integration of molecular processes in each individual cell, and single-cell (agent) based models [32], [30], [143]. Works by Schliess [139], [101] have been highlighted in editorials.

Mathematical modeling of protein aggregation is a relatively recent domain, only a few other groups have emerged yet; among them we can cite the Inria team Dracula, with whom we are in close contact, and e.g., the work by Jean-Michel Coron (Sorbonne Université) and Monique Chyba (Hawaii, USA) in control, and Suzanne Sindi (USA) for the modeling of the yeast prion. We have interactions with all these groups and organized a workshop in June 2017, gathering both the biophysics and applied mathematics communities.

Scientific achievements

Amyloid disease
Application to protein aggregation in amyloid diseases is a long-standing interest of Mamba, dating back to 2010 [85], and developed through the collaboration with Human Rezaei's team at Inra. More recently, with Wei-Feng Xue in Canterbury, we investigated the intrinsic variability among identical experiments of nucleation [93], [100], Sarah Eugène's Ph.D subject (co-supervised by Philippe Robert) [99].

In collaboration with Tom Banks first [69], [70] and then Philippe Moireau, we developed quantitative comparisons between model and data. Through data assimilation and statistical methods [63], we proposed new models and mechanisms.

Biological control of arboviroses
Sterile Insect Technique (SIT) [98] is a biological control method relying on massive releases of sterile male insects into the wild. The latter compete with wild males to mate with the females, and induce no offspring to the latter, thus reducing the next generation's population. This can result in a progressive reduction, or even disparition, of the target population.

A related technique is based on the infection by *Wolbachia* [104]. This symbiotic bacterium is maternally transmitted from infected females to their offspring, but induces *cytoplasmic incompatibility* [141], [80]: mating between infected males and uninfected females gives no offspring. Releases of *Wolbachia* infected males alone is thus comparable to classical SIT.

On the other hand, releasing both infected males and females in sufficient quantity may result in infection of the wild population. This gives rise to an interesting new control principle, as *Wolbachia* has been shown to severely reduce the insect vectorial ability to transmit dengue, zika or chikungunya, indirectly by lifespan and fertility reduction, and directly by reducing the ability of the viruses to proliferate within the organism [121].

We proposed new insights on the practical and theoretical issues raised by the implementation of the previous methods.

Wound healing 1: epithelial tissues
We studied cell motion in epithelial gap closure, a form of collective cell migration that is a very widespread phenomenon both during development and adult life - it is essential for both the formation and for the maintenance of epithelial layers. Due to their importance, *in vivo* wound healing and morphogenetic movements involving closure of holes in epithelia have been the object of many studies. In our works [1] we considered wound healing and epithelial gap closure in both in vivo (in particular drosophila pupa) and in vitro (MDCK cell and human keratinocytes). We found some similarities in the geometry dependence of the wound closure strategies between these two situations, indicating the existence of conserved mechanisms that should be widespread across living beings. We are concentrating on the study of actin cable formation.

Wound healing 2: adipose tissues
After injury, if regeneration can be observed in hydra, planaria and some vertebrates, regeneration is rare in mammals and particularly in humans. In this research axis, we investigated the mechanisms by which biological tissues recover after injury. We explored this question on adipose tissue, using the mathematical framework recently developed in [134]. Our assumption is that simple mechanical cues between the Extra-Cellular Matrix (ECM) and differentiated cells can explain adipose tissue morphogenesis and that regeneration requires after injury the same mechanisms. We validated this hypothesis by means of a two-dimensional Individual Based Model (IBM) of interacting adipocytes and ECM fiber elements [135]. The model successfully generated regeneration or scar formation as functions of few key parameters, and seemed to indicate that the fate of injury outcome could be mainly due to ECM rigidity.

Modeling of morphogen diffusion in *Drosophila* oogenesis
In collaboration with a team of developmental biologists of Rutgers University (Camden, New Jersey), we have built a model for the diffusion of the Gurken morphogen during *Drosophila* oogenesis, taking into account a wide variety of biological mechanisms such as diffusion of the morphogen, reactions of components of the EGFR signaling pathway, movement of the source of morphogen, shift of the overlying follicle cells and growth of the egg chamber. This model, together with a complete numerical code developed in Matlab, provides a tool to understand how each mechanism influences the signal distribution. The overall aim of the project is to use this tool to guide future experiments, and to understand what mechanisms contribute to the different distributions of signal among species.

Bacterial population growth
We exploited all the methods developed to estimate the division rate of a population (see axis 3) to address a seminal question of biology: is it a size-sensing or a timing mechanism which triggers bacterial growth? In [138], we showed that a sizer model is robust and fits the data well. Several studies from other groups came at the same time, showing a renewed interest on a question dated back to Jacques Monod's PhD thesis (1941). Of special interest is the "adder" model, for which we are currently developing new estimation methods.

A quantitative high resolution computational mechanics cell model for growing and regenerating tissues

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[1]ravasio:hal-01245750, vedula:hal-01298859

Mathematical models are increasingly designed to guide experiments in biology, biotechnology, as well as to assist in medical decision-making. They are in particular important to understand emergent collective cell behavior. For this purpose, the models, despite still abstractions of reality, need to be quantitative in all aspects relevant for the question of interest. During the regeneration of liver after drug-induced depletion of hepatocytes surviving dividing and migrating hepatocytes must squeeze through a blood vessel network to fill the emerged lesions. Here, the cells' response to mechanical stress might significantly impact on the regeneration process. We developed a 3D high-resolution cell-based model integrating information from measurements in order to obtain a refined quantitative understanding of the cell-biomechanical impact on the closure of drug-induced lesions in liver. Our model represents each cell individually, constructed as a physically scalable network of viscoelastic elements, capable of mimicking realistic cell deformation and supplying information at subcellular scales. The cells have the capability to migrate, grow and divide, and infer the nature of their mechanical elements and their parameters from comparisons with optical stretcher experiments. Due to triangulation of the cell surface, interactions of cells with arbitrarily shaped (triangulated) structures such as blood vessels can be captured naturally. Comparing our simulations with those of so-called center-based models, in which cells have a rigid shape and forces are exerted between cell centers, we find that the migration forces a cell needs to exert on its environment to close a tissue lesion, is much smaller than predicted by center-based models. This effect is expected to be even more present in chronic liver disease, where tissue stiffens and excess collagen narrows pores for cells to squeeze through [44].

Main collaborators: Stefan Höhme, Univ. Leipzig; Josef Käs, Univ. Leipzig.

Modeling the extracellular matrix in multicellular organization and liver regeneration:
An important step has been undertaken to integrate an explicit model of collagen networks in liver and other tissues. The mechanical model of collagen fibers uses linear and rotational springs to represent collagen fibers and collagen network taking into account the stretching and bending energy of the collagen network. The model has been validated by direct comparison to experiments where a force has been excerted on a single collagen fiber, as well as to shear experiments. In a next step, this collagen model has been incorporated into the previous lobule model to simulate spatio-temporal pattern of the ECM in the lobule. One key objective is a model of fibrosis development, whereby fibrotic streets form. So far, not coherent model exist but a number of hypotheses that will be implemented and tested versus data.

Main collaborators: Steven Dooley, Seddik Hammad, Univ. Mannheim; JG Hengstler, IfADo.

Models of flow in liver
Also for the liver, a model for bile salts transport has been developed. The current hypothesis is that bile salt excreted by hepatocytes into bile canaliculi, are transported within canaliculi by convection through the canal of hering to the bilary ducts. In close iterations with experiments and by image based modeling runing simulations directly in reconstructed 3D volume data sets, we test different alternative mechanisms of bile transport.

The blood flow model of the individual liver lobule, the smallest anatomical and functional repetitive unit of liver has been embedded in an electrical analogue model for the whole model hemodynamics to compute the impact of architectural changes at the lobule level as they occur after partial hepatectomy on the whole body hemodynamics. At the lobule level, the impact of capillary diameters on the flow have been studied under consideration of the hematocrit value (the volume fraction of red blood cells).

Collaborators: Chloé Aubert, UPMC, I. Vignon-Clementel, REO, Jan G. Henstler and Natiket Vartak, IfADo, Eric Vibert, Hopital Paul Brousse, Villejuif

Liver development
The deformable cell model is being used to establish a model of bile duct formation. Bile ducts from at the portal veins as a consequence of an interaction of cholagiocytes, aligning the mesenchyme of the portal vein, and hepatoblasts surrounding the portal veins. Hepatoblasts are a pre-stage of hepatocytes. Current biological hypotheses speculate that bile ducts may either emerge from proliferation of the hepatoblast layer that is in contact to cholangiocytes, leading to formation of a lumen by buckling, by attraction of water a positions

where cholangiocytes secret mucin, or by apical contraction of hepatoblasts within the layer in contact to the cholangiocytes. The simulations are performed with the deformable cell model.

Collaborators: Frederic Lemaigre, De Duve Institut, Brussels, Anne Dubart-Kupperschmitt, Hopital Paul Brousse.

Image processing, analysis and quantification of tissue microarchitecture
At the interface between experiment and modeling we pursue a number of projects on image analysis and quantification. Such information in the past often served to generate hypotheses of the mechanisms underlying image sequences in time, which then could be turned in a mathematical model to verify, which hypotheses are sufficient to explain the image data. Several image analysis projects focus on the liver. (1.) Bile microinfacts have been found to be initiated by rupture of the apical hepatocyte membrane leading to shunting from bile canaliculi to the blood capillaries. This is followed by massive increase of the immune cells as could be quantified by analysis of intravital micrographs. For every frame in the video, a binary mask that most likely resemble detected immune cells were obtained. The process started by applying suitable linear and non-linear filters to highlight structure of interest and remove noise. Morphological operations and blob analysis was finally utilized to locate and count the cells. With the help of an expert, the confusion matrix was finally established to assess the quality of the segmentation and the obtained results (Ghallab et. al., J. Hepat. 2018; https://aasldpubs.onlinelibrary.wiley.com/doi/full/10.1002/hep.30213. [14]) (2.) In a second project, the CYP – enzyme distribution is quantified after repetitive administration of CCl4. After single overdose of CCl4, the liver shows a peri-central liver lobule (smallest repetitive anatomical unit of liver) necrosis. This pattern changes in repetitive dosing and leads to chronic disease stages and sometimes eventually to either hepatocellular carcinoma [15] or acute-on-chronic liver failure (ACLF), a disease condition with often-lethal outcome. Data from whole-slide scans is analyzed to serve to develop a mathematical model of ACLF. (3.) A similar strategy is pursued for fibrosis formation through high fat diet both by image analysis of mouse and human data, aiming at a mathematical lobule model based on a deformable cell model. Here currently images are analyzed to quantify microarchitectural modifications as a consequence of Western Diet (a high fat diet generating a disease condition reminiscent of NAFLD in human. (4.) TiQuant-algorithms have been used to analyze micro-and macrovascular alterations in cirrhosis [125] and (5.) tissue modifications after PHx [82].

Main collaborators: Ahmed Ghallab, Jan G. Hengstler, IfADo; Ursula Klingmüller, DKFZ Heidelberg; Steven Dooley, Univ. Hospital Mannheim; Percy Knolle, Helmholz Inst. Munich, Joachim Bode, Univ. Hospital Düsseldorf, Christian Trautwein, Univ. Hosp. Aachen; P. Seegers (Ghent University); Eric Vibert (Hopital Paul Brousse).

Relating imaging on microscopic scales with imaging on macroscopic scales: From Diffusion-Weighted MRI Calibrated With Histological Data: an Example From Lung Cancer
Diffusion-weighted magnetic resonance imaging (DWI) is a key non-invasive imaging technique for cancer diagnosis and tumor treatment assessment, reflecting Brownian movement of water molecules in tissues. Since densely packed cells restrict molecule mobility, tumor tissues produce usually higher signal (less attenuated signal) on isotropic maps compared with normal tissues. However, no general quantitative relation between DWI data and the cell density has been established. In order to link low-resolution clinical cross-sectional data with high resolution histological information, we developed an image processing and analysis chain, which was used to study the correlation between the diffusion coefficient (D value) estimated from DWI and tumor cellularity from serial histological slides of a resected non-small cell lung cancer tumor. Color deconvolution followed by cell nuclei segmentation was performed on digitized histological images to determine local and cell-type specific 2d (two-dimensional) densities. From these, the 3d cell density was inferred by a model-based sampling technique, which is necessary for the calculation of local and global 3d tumor cell count. Next, DWI sequence information was overlaid with high resolution CT data and the resected histology using prominent anatomical hallmarks for co-registration of histology tissue blocks and non-invasive imaging modalities' data. The integration of cell numbers information and DWI data derived from different tumor areas revealed a clear negative correlation between cell density and D value. Importantly, spatial tumor cell density can be calculated based on DWI data. In summary, our results demonstrate that tumor cell count and heterogeneity can be predicted from DWI data, which may open new opportunities for personalized diagnosis

and therapy optimization [145]. The work of that paper has been further advanced to adapt the procedures for clinical use (in preparation).

Collaborations

- Biological control of arboviroses: **Nicolas Vauchelet** (Université Paris 13); **Grégoire Nadin** (LJLL, Sorbonne Université); **Yannick Privat** (Université de Strasbourg); **D. Villela, C. Struchiner** (Fiocruz, Brazil); **Jorge Zubelli** (IMPA, Brazil); **Alain Rapaport** (INRA-Montpellier), **Y. Dumont** (CIRAD-Montpellier); **Ch. Schaerer, P. Pérez-Estigarribia** (UNA, Paraguay), **O. Vasilieva** (Universidad del Valle, Cali, Colombia), **D. Cardona-Salgado** (Universidad Autónoma de Occidente, Cali, Colombia).

- Protein aggregation in amyloid diseases: **Human Rezaei**'s team at Inra Jouy-en-Josas (France) and **W-F Xue**'s team in at university of Kent (Great Britain); **Tom Banks** at the North Carolina State University (USA) and **Philippe Moireau** (M3DISIM)

- Bacterial growth and division: **Lydia Robert**, Sorbonne Université (France)

- Liver research & toxicology: **JG. Hengstler** group (IfADo, Dortmund, Germany); **R. Gebhardt** (Univ. Leipzig); **U. Klingmueller** (DKFZ, Heidelberg); **Irène Vignon-Clementel** (Inria, REO)

- Wound healing: **Patrizia Bagnerini** (Genova, Numerical methods), **Benoît Ladoux** (Institut Jacques Monod et Mechanobiology Institute Singapore, Biophysics) and **Antonio Jacinto** (CEDOC, Lisbon, Biology and Medicine). (Adipose tissue regeneration) team of **L. Casteilla** (StromaLab, Toulouse)

- Diffusion of morphogen: Center for Computational and Integrative Biology, Rutgers University (Camden, New Jersey), joint work with Professor Nir Yakoby's Drosophila Laboratory

- Linking micro and macro-image information: Oliver Sedlaczek, Univ. and DKFZ Heidelberg, Kai Breuhahn, Univ. Heidelberg.

5. Highlights of the Year

5.1. Highlights of the Year

We welcome a new team member, Nastassia Pouradier-Duteil, junior research scientist since September 2018.

We welcome Ayman Moussa in delegation since September 2018; he defended his habilitation thesis on December 13th.

Marie Doumic finished her two-year sabbatical stay in September 2018.

Jean Clairambault is emeritus DR since March 2018.

5.1.1. *Awards*

In December 5, 2017, Benoit Perthame has been elected at the Académie des Sciences, and was received in the Académie on May 28, 2018.

Christian Schmeiser, associate member of Mamba through the associated team MaMoCeMa with the university of Vienna, being the laureate of the "chaire d'excellence" of the FSMP, is for six months in Paris (september 2018 to february 2019).

6. New Software and Platforms

6.1. TiQuant

Tissue Quantifier
KEYWORDS: Systems Biology - Bioinformatics - Biology - Physiology

FUNCTIONAL DESCRIPTION: Systems biology and medicine on histological scales require quantification of images from histological image modalities such as confocal laser scanning or bright field microscopy. The latter can be used to calibrate the initial state of a mathematical model, and to evaluate its explanatory value, which hitherto has been little recognized. We generated a software for image analysis of histological material and demonstrated its use in analysing liver confocal micrografts, called TiQuant (Tissue Quantifier). The software is part of an analysis chain detailing protocols of imaging, image processing and analysis in liver tissue, permitting 3D reconstructions of liver lobules down to a resolution of less than a micrometer.

- Author: Dirk Drasdo
- Contact: Dirk Drasdo

6.2. TiSim

Tissue Simulator

KEYWORDS: Systems Biology - Bioinformatics - Biology - Physiology

SCIENTIFIC DESCRIPTION: TiSim (Tissue Simulator) is a versatile and efficient simulation environment for tissue models. TiSim is a software for agent-based models of multicellular systems. It permits model development with center-based models and deformable cell models, it contains modules for monolayer and multicellular spheroid simulations as well as for simulations of liver lobules. Besides agent-based simulations, the flow of blood and the transport of molecules can be modelled in the extracellular space, intracellular processes such as signal transduction and metabolism can be simulated, for example over an interface permitting integration of SBML-formulated ODE models. TiSim is written in modern C++ , keeping central model constituents in modules to be able to reuse them as building blocks for new models. For user interaction, the GUI Framework Qt is used in combination with OpenGL for visualisation. The simulation code is in the process of being published. The modeling strategy and approaches slowly reach systems medicine and toxicology. The diffusion of software is a fundamental component as it provides the models that are complex and difficult to implement (implementing a liver lobule model from scratch takes about 2-2.5yrs) in form of a software to the developer and users who like to build upon them. This increases significantly the speed of implementing new models. Moreover, standardization is indispensible as it permits coupling different software tools that may have implemented models at different scales / levels.

FUNCTIONAL DESCRIPTION: TiSim is a software that permits agent-based simulations of multicellular systems. - center-based lattice-free agent-based model - modular - C++, Qt, OpenGL, GUI, batch mode - permits multiscale simulations by integration of molecular pathways (for signaling, metabolisms, drug) into each individual cell - applications so far: monolayer growth, multicellular spheroids - Boolean networks (development time = coding time (60 MMs) + model development time (264 MMs)) - in follow-up version 1: - liver lobule regeneration - SBML interface - in follow-up version 2: - deformable cell model (by triangulation of cell surface) - deformable rod models - extracellular matrix - vascular flow and transport TiSim can be directly fed by processed image data from TiQuant.

- Participants: Andreas Buttenschoen, Dirk Drasdo, Eugenio Lella, Géraldine Cellière, Johannes Neitsch, Margaretha Palm, Nick Jagiella, Noémie Boissier, Paul Van Liedekerke, Stefan Hoehme and Tim Johann
- Partner: IZBI, Université de Leipzig
- Contact: Dirk Drasdo

6.3. Platforms

6.3.1. TiSim

New side branches have been developed that integrate the deformable cell model and extracellular matrix model in the TiSim software.

6.3.2. TiQuant

The software has been further extended for machine learning components.

7. New Results

7.1. Modelling Polymerization Processes

Nucleation Phenomena.
A new stochastic model of polymerization including the nucleation has been analyzed in [4]. A Functional Central Limit Theorem for the Becker-Döring model in an infinite dimensional state space is established in [25].

An oscillatory model of polymerisation-depolymerisation.
In 2017, we evidenced the presence of several polymeric species by using data assimilation methods to fit experimental data from H. Rezaei's lab [64]. In collaboration with Klemens Fellner from the university of Graz, we now propose a new model, variant of the Becker-Döring system but containing two monomeric species, capable of displaying sustained though damped oscillations [39].

Time asymptotics for nucleation, growth and division equations.
We revisited the well-known Lifshitz-Slyozov model, which takes into account only polymerisation and depolymerisation, and progressively enriched the model. Taking into account depolymerisation and fragmentation reaction term may surprisingly stabilisde the system, since a steady size-distribution of polymers may then emerge, so that "Ostwald ripening" does not happen [8].

Cell population dynamics and its control
The PhD thesis work of Camille Pouchol (co-supervisors Jean Clairambault, Michèle Sabbah, INSERM, and Emmanuel Trélat, Inria CAGE and LJLL) has been continued, leading after his first article published in the J. Maths Pures Appl. [136], summarised in [31], to his PhD defence in June [1], and to a diversification of his research activities in various directions related to population dynamics and optimal control with Antoine Olivier, Emmanuel Trélat and Enrique Zuazua [51], [56] or to more general questions [55].

Measure solutions for the growth-fragmentation equation
As recalled in the section "Foundations", entropy methods for population dynamics have been successfully developed around B. Perthame and co-authors. We recently extend such methods to the growth-fragmentation equation, in collaboration with P. Gwiazda, E. Wiedemann and T. Debiec [40], using the framework of generalised Young measures.

7.2. Large Stochastic Networks

The equilibrium properties of allocation algorithms for networks with a large number of nodes with finite capacity are investigated in [46] and in [60].

7.3. Control Strategies for Sterile Insect Techniques

We proposed different models to serve as a basis for the design of control strategies relying on releases of sterile male mosquitoes (*Aedes spp*) and aiming at elimination of wild vector population. Different types of releases were considered (constant, periodic or impulsive) and sufficient conditions to reach elimination were provided in each case [57], [3], [35]. We also estimated sufficient and minimal treatment times. A feedback approach was introduced, in which the impulse amplitude is chosen as a function of the actual wild population [57], [3], [35].

7.4. Optimal replacement strategies, application to Wolbachia

We modelled and designed optimal release control strategy with the help of a least square problem. In a nutshell, one wants to minimize the number of uninfected mosquitoes at a given time horizon, under relevant biological constraints. We derived properties of optimal controls and studied a limit problem providing useful asymptotic properties of optimal controls [49], [3].

7.5. Oscillatory regimes in population models

Understanding mosquitoes life cycle is of great interest presently because of the increasing impact of vector borne diseases. Observations yields evidence of oscillations in these populations independent of seasonality, still unexplained. We proposed [58], [3] a simple mathematical model of egg hatching enhancement by larvae which produces such oscillations that conveys a possible explanation.

On the other hand, population oscillations may be induced by seasonal changes. We considered a biological population whose environment varies periodically in time, exhibiting two very different "seasons", favorable and unfavorable. We addressed the following question: the system's period being fixed, under what conditions does there exist a critical duration above which the population cannot sustain and extincts, and below which the system converges to a unique periodic and positive solution? We obtained [59], [3] sufficient conditions for such a property to occur for monotone differential models with concave nonlinearities, and applied the obtained criterion to a two-dimensional model featuring juvenile and adult insect populations.

7.6. Feedback control principles for population replacement by Wolbachia

The issue of effective scheduling of the releases of *Wolbachia*-infected mosquitoes is an interesting problem for Control theory. Having in mind the important uncertainties present in the dynamics of the two populations in interaction, we attempted to identify general ideas for building release strategies, which should apply to several models and situations [34]. These principles were exemplified by two interval observer-based feedback control laws whose stabilizing properties were demonstrated when applied to a model retrieved from [76].

7.7. Bacterial motion by run and tumble

Collective motion of chemotactic bacteria such as Escherichia coli relies, at the individual level, on a continuous reorientation by runs and tumbles. It has been established that the length of run is decided by a stiff response to a temporal sensing of chemical cues along the pathway. We describe in [21] a novel mechanism for pattern formation stemming from the stiffness of chemotactic response relying on a kinetic chemotaxis model which includes a recently discovered formalism for the bacterial chemotaxis. We prove instability both for a microscopic description in the space-velocity space and for the macroscopic equation, a flux-limited Keller-Segel equation, which has attracted much attention recently. A remarkable property is that the unstable frequencies remain bounded, as it is the case in Turing instability. Numerical illustrations based on a powerful Monte Carlo method show that the stationary homogeneous state of population density is destabilized and periodic patterns are generated in realistic ranges of parameters. These theoretical developments are in accordance with several biological observations.

This motivates also our study of traveling wave and aggregation in population dynamics of chemotactic cells based on the FLKS model with a population growth term [7]. Our study includes both numerical and theoretical contributions. In the numerical part, we uncover a variety of solution types in the one-dimensional FLKS model additionally to standard Fisher/KPP type traveling wave. The remarkable result is a counter-intuitive backward traveling wave, where the population density initially saturated in a stable state transits toward an un- stable state in the local population dynamics. Unexpectedly, we also find that the backward traveling wave solution transits to a localized spiky solution as increasing the stiffness of chemotactic response. In the theoretical part, we obtain a novel analytic formula for the minimum traveling speed which includes the counter-balancing effect of chemotactic drift vs. reproduction/diffusion in the propagating front. The front propagation speeds of numerical results only slightly deviate from the minimum traveling speeds, except for the localized spiky solutions, even for the backward traveling waves. We also discover an analytic solution of unimodal traveling wave in the large-stiffness limit, which is certainly unstable but exists in a certain range of parameters.

7.8. Numerical methods for cell aggregation by chemotaxis

Three-dimensional cultures of cells are gaining popularity as an in vitro improvement over 2D Petri dishes. In many such experiments, cells have been found to organize in aggregates. We present new results of three-

dimensional in vitro cultures of breast cancer cells exhibiting patterns. Understanding their formation is of particular interest in the context of cancer since metastases have been shown to be created by cells moving in clusters. In the paper [37], we propose that the main mechanism which leads to the emergence of patterns is chemotaxis, i.e., oriented movement of cells towards high concentration zones of a signal emitted by the cells themselves. Studying a Keller-Segel PDE system to model chemotactical auto-organization of cells, we prove that it is subject to Turing instability if a time-dependent condition holds. This result is illustrated by two-dimensional simulations of the model showing spheroidal patterns. They are qualitatively compared to the biological results and their variability is discussed both theoretically and numerically.

This motivates to study parabolic-elliptic Keller-Segel equation with sensitivity saturation, because of its pattern formation ability, is a challenge for numerical simulations. We provide in [16] two finite-volume schemes that are shown to preserve, at the discrete level, the fundamental properties of the solutions, namely energy dissipation, steady states, positivity and conservation of total mass. These requirements happen to be critical when it comes to distinguishing between discrete steady states, Turing unstable transient states, numerical artifacts or approximate steady states as obtained by a simple upwind approach. These schemes are obtained either by following closely the gradient flow structure or by a proper exponential rewriting inspired by the Scharfetter-Gummel discretization. An interesting fact is that upwind is also necessary for all the expected properties to be preserved at the semi-discrete level. These schemes are extended to the fully discrete level and this leads us to tune precisely the terms according to explicit or implicit discretizations. Using some appropriate monotonicity properties (reminiscent of the maximum principle), we prove well-posedness for the scheme as well as all the other requirements. Numerical implementations and simulations illustrate the respective advantages of the three methods we compare.

7.9. Focus on cancer

Modelling Acute Myeloid Leukaemia (AML) and its control by anticancer drugs by PDEs and Delay Differential equations
This theme has continued to be developed in collaboration with Catherine Bonnet, Inria DISCO (Saclay) [12], [29]. Without control by drugs, but with representation of mutualistic interactions between tumor cells and their surrounding support stroll cells, it has also, in collaboration with Delphine Salort and Thierry Jaffredo (LCQB-IBPS) given rise to a recent work by Thanh Nam Nguyen, hired as HTE and ERC postdoctoral fellow at LCQB, submitted as full article [50].

Adaptive dynamics setting to model and circumvent evolution towards drug resistance in cancer by optimal control
The research topic "Evolution and cancer", designed in the framework of adaptive dynamics to represent and overcome acquired drug resistance in cancer, initiated in [119], [118] and later continued in [90], [89], [117], has been recently summarised in [31] and has been the object of the PhD thesis work of Camille Pouchol, see above "Cell population dynamics and its control" . It is now oriented, thanks to work underway by Cécile Carrère, Jean Clairambault, Tommaso Lorenzi and Grégoire Nadin, in particular towards the mathematical representation of *bet hedging* in cancer, namely a supposed optimal strategy consisting for cancer cell populations under life-threatening cell stress in diversifying their phenotypes according to several resistance mechanisms, such as overexpression of ABC transporters (P-glycoprotein and many others), of DNA repair enzymes or of intracellular detoxication processes. According to different deadly insults the cancer cell population is exposed to, some phenotypes may be selected, any such successful subpopulation being able to store the cell population genome (or subclones of it if the cell population is already genetically heterogeneous) and make it amenable to survival and renewed replication.

Philosophy of cancer biology

This new research topic in Mamba, dedicated to explore possibly underinvestigated, from the mathematical modelling point of view, parts of the field of cancer growth, evolution and therapy, has been the object of a presentation by Jean Clairambault at the recent workshop "Philosophy of cancer biology' (https://www.philinbiomed.org/event/philosophy-of-cancer-biology-workshop/). This workshop gathered most members worldwide of this small, but very active in publishing, community of philosophers of science whose field of research is "philosophy of cancer", as they call it themselves. This topic offers a clear point of convergence between mathematics, biology and social and human sciences.

7.10. Deformable Cell Modeling: biomechanics and Liver regeneration

- Biomechanically mediated growth control of cancer cells The key intriguing novelty was that the same agent-based model after a single parameter has been calibrated with growth data for multicellular spheroids without application of external mechanical stress by adapting a single parameter, permitted to correctly predict the growth speed of multicellular spheroids of 5 different cell lines subject of external mechanical stress. Hereby the same mechanical growth control stress function was used without any modification [44]. The prediction turned out to be correct independent of the experimental method used to exert the stress, whereby once a mechanical capsule has been used, once dextran has been used in the experiments.

- Regeneration of liver with the Deformable Cell Model. The key novelty was the implementation of the model itself, but an interesting novel result is that the DCM permits closure of a pericentral liver lobule lesion generated by drug-induced damage with about 5 times smaller active migration force due to the ability of the cell to strongly deform and squeeze into narrow spaces between the capillaries. This finding stresses that a precise mechanical description is important in view of quantitatively correct modeling results [142]. The deformable cell model however could be used to calibrate the interaction forces of the computationally much cheaper center-based model to arrive at almost the same results.

8. Bilateral Contracts and Grants with Industry

8.1. Bilateral Contracts with Industry

Contract with Orange labs (2016-2018) for Veronica Quintuna's PhD. See Reference [2].

9. Partnerships and Cooperations

9.1. National Initiatives

9.1.1. ANR

9.1.1.1. ANR Blanc 2014-2018 "Kibord"

This project gathers several members of the MAMBA team together with the ENS Cachan and Université Paris-Dauphine on the mathematical study of PDE models with application to biology.

9.1.1.2. ANR iLITE 2016 - 2020

Jean-Charles Duclos-Vallée, Paul Brousse Hospital, Villejuif. Partners are several departments in Paul Brousse Hospital, ENS Cachan, University of Compiègne and several companies all over France, and REO team, Inria Paris. The pursued objective is the bioengineering design of an artificial liver intended for liver replacement.

9.1.1.3. ANR InTelo 2017-2020

Telomere dynamics, headed by Teresa Teixeira (IBPC, Paris).

9.1.1.4. INCa/DGOS; PRT-K 2018-2021

Khê HOANG-XUAN, Hôpital Universitaire La Pitié Salpêtrière, Paris. Mathematical modeling at micro and macroscopic level of primary central nervous system lymphomas (PCNSL).

9.1.2. ITMO Cancer 2016 - 2020, HTE call (heterogeneity of tumours in their ecosystems)

9.1.2.1. ITMO Cancer EcoAML

Early leukaemogenesis in Acute Myelogenous Leukaemia (AML), 8 teams headed by François Delhommeau (CDR St Antoine, Paris).

9.1.2.2. ITMO Cancer MoGlImaging

Treatment-induced treatment resistance and heterogeneity in glioblastoma, 8 teams headed by Elizabeth Moyal (INSERM, Toulouse).

9.2. European Initiatives

9.2.1. Collaborations in European Programs, Except FP7 & H2020

Program: Celtic+

Project acronym: Sendate

Project title:Secure Networking for a Data Center Cloud in Europe

April 2016/May 2019

Coordinator: Nokia

Other partners: Siemens, IMT, ...

9.3. International Initiatives

9.3.1. Inria Associate Teams Not Involved in an Inria International Labs

9.3.1.1. MaMoCeMa

Title: Mathematical modeling of cell motility and of autophagy

International Partner (Institution - Laboratory - Researcher):

University of Vienna (Austria) - Wolfgang Pauli Institute - Christian Schmeiser

Start year: 2018

Numerous fruitful collaborations have been developed these last years between the WPI and the Inria team MAMBA. Diane Peurichard – newly recruited permanent member of the team MAMBA – worked two years (2016-2017) with Christian Schmeiser – member of the present project – through a post-doctoral contract at the university of Vienna. In collaboration with the biologists of IST, they developed mathematical tools to understand how cells move through adhesion-based and adhesion-free motion with applications in cancer development, prevalent theme of the team MAMBA. Collaborations WPI-MAMBA are presently maintained and ensured by the sabbatical of Marie Doumic – MAMBA team leader –, working at the university of Vienna with Christian Schmeiser and the PhD student Julia Delacour. They have initiated a collaboration on the mathematical modeling of autophagy, which requires both C. Schmeiser's expertise in biomechanics and M. Doumic's knowledge on aggregation processes. This team will also benefit of the strong links that C. Schmeiser has developed with the two biologists teams of S. Martens (on autophagy) and M. Sixt (on cell movement).

Of note, C. Schmeiser has been a laureate for the "Chaire d'excellence" program of the FSMP. As such, he is for six months in Paris, and delivered a course at IHP on entropy methods. Many of his students and collaborators visited him (D. Oelz, G. Jankowiak, L. Kanzler, G. Favre, L. Neumann...), and participated to a joint Mamba-MaMoCeMa meeting on December 6th, still strengthening our links.

9.3.2. Participation in Other International Programs

9.3.2.1. International Initiatives

ECOS Nord C17M01

Title: News methods for controle of dengue and arobivroses epidemics

International Partner (Institution - Laboratory - Researcher):

Universidad del Valle (Colombia) - Department of Mathematics - Olga Vasilieva

Duration: 2017 - 2019

Start year: 2017

The overall goal of the project is the development of mathematical models and theory-based control methods, contributing to the improvement of epidemiological surveillance and the control of dengue and other serious diseases transmitted by mosquitoes Aedes aegypti (chikungunya, yellow fever, zika fever). More specifically, it :

- Develops modeling framework for the biological control of mosquito populations (through the use of natural predators, Wolbachia bacteria etc.).

- Proposes and evaluates control strategies based on the use of biological agents and on their possible combinations with traditional control measures (such as removal of reproduction, spraying insecticides and / or larvicides, use of mosquito nets, repellents, etc.).

- Compares the results of biological control strategies (and their combinations) with those of traditional control using a cost / efficiency approach.

- Includes in the developments the spatial aspects of the questions above.

BMBF (Germany) / LiSym; 2016-2020 LiSym addresses liver diseases and regeneration, namely, steatosis, fibrosis and cirrhosis, and acute on chronic liver failure. Dirk Drasdo is co-coordinator of one sub-project, participant in one of the other ones, and member of the leadership board

BMBF (Germany) / MSDILI; 2016-2019 MS-DILI addresses multiscale modeling of drug-induced liver disease focusing on the role of APAP. Dirk Drasdo participates in this project.

9.4. International Research Visitors

9.4.1. Visits of International Scientists

- Prof. Olga Vasilieva (Universidade del Valle, Cali, Colombia) was invited during three weeks, together with Edwin Bairros, PhD student.
- Prof. Yukihiko Nakata (Shimane University, Matsue, Japan) was hosted during one week in the framework of the French program Exploration France.
- Prof. C. Schmeiser (university of Vienna, Austria) was visiting during four month, from september 2018, and should stay until february 2019.
- Prof. D. Oelz (university of Queensland, Australia) visited from Dec. 5th to Dec. 21st.
- Jieling Zhao, Postdoc from IfADo
- Paul van Liedekerke, Research engineer from IfADo

9.4.1.1. Internships

Ismael Gonzalez Valverde (University of Zaragoza) visited our team for 3 months working on implementation of the meshing of liver micro-structures in modeling of liver regeneration within TiSim.

9.4.2. Visits to International Teams

9.4.2.1. Sabbatical programme

Marie Doumic was in Vienna for a sabbatical stay until July 2018.

10. Dissemination

10.1. Promoting Scientific Activities

10.1.1. Scientific Events Organisation

10.1.1.1. General Chair, Scientific Chair

- Jean Clairambault, with Jean-Frédéric Gerbeau, Huaxiong Huang, Benoît Perthame and Sivobal Sivaloganathan: organisers of the First Inria-Sorbonne-Université-Fields Institute international workshop on mathematics in medicine, Fields Institute, Toronto, January 31 to February 2, 2018. http://www.fields.utoronto.ca/activities/17-18/math-medicine

- Jean Clairambault, with Guillemette Chapuisat, Florence Hubert, Urszula Ledzewicz and Vitaly Volpert: organisers of the International 5-day workshop on Mathematical perspectives in the biology and therapeutics of cancer, CIRM Luminy, July 9-13, 2018. https://mathscancer.sciencesconf.org/

- Jean Clairambault, with Tomás Alarcón and Thomas Hillen: organisers of the BIRS-CMO 5-day workshop on Mathematical Challenges in the Analysis of Continuum Models for Cancer Growth, Evolution and Therapy (18w5115), Casa Matemática Oaxaca (Mexico), November 25-30, 2018. http://www.birs.ca/events/2018/5-day-workshops/18w5115

- Benoît Perthame, Luis Almeida, Diane Peurichard and Delphine Salort: organizers of the workshop 'Asymptotic approaches to spatial and dynamical organizations', july 2018, LJLL, Sorbonne Université, and organizers of the math-bio working group at LJLL, Sorbonne Université

- Diane Peurichard, Dirk Drasdo: organizers of the internal seminar 'Open MAMBA seminar' (https://team.inria.fr/mamba/open-mamba-seminar/)

- Marie Doumic, with Doron Levy (U. of Maryland, USA), M. Bergmann (Med. University of Vienna) and N. Mauser (Wolfgang Pauli Institute, Vienna) organised a workshop on "Mathematical Models in Cancer", on July 20th and 21st, 2018.

- Marie Doumic, together with J. Haskovec (KAUST Univ., Saoudi Arabia), M.-T. Wolfram (Univ. of Warwick, UK), K. Fellner (Univ. of Graz, Austria) and L. Neumann (U. of Innsbruck, Austria), organised a workshop on "Applied PDEs and kinetic equations: from physics to life sciences and beyond", in the honor of C. Schmeiser's 60th birthday.

- L. Almeida, B. Perthame, D. Peurichard and D. Salort have organized the international conference "Asymptotic approach to spatial and dynamical organizations", 4-6 july 2018 (60 participants)

10.1.2. Scientific Events Selection

10.1.2.1. Member of the Conference Program Committees

- Philippe Robert was in the PC of the conference "Stochastic Networks" held in Edimburgh 25-29 June 2018.

- Pierre-Alexandre Bliman was in the Editorial Board of the conference "European Control Conference", Limassol, 12-15 June 2018.

- Dirk Drasdo was member of the Program committee of the SBMC 2018 (Bremen, Germany), July 4-6, 2018.

10.1.2.2. Reviewer

- Pierre-Alexandre Bliman, reviewer for the conferences IEEE Conference on Decision Control, European Control Conference, Indian Control Conference, Joint 9th IFAC Symposium on Robust Control Design and 2nd IFAC Workshop on Linear Parameter Varying Systems

10.1.3. Journal

10.1.3.1. Member of the Editorial Boards

- Philippe Robert is Associate Editor of the journal "Queueing Systems, Theory and Applications".
- Benoît Perthame is co-editor in chief of Acta Applicandae Mathematicae (Springer).
- Dirk Drasdo is associate editorial member of J. Theor. Biol. and Royal Society Open Science.
- Luis Almeida is Associate Editor of the Journal of Dynamics and Games AIMS.

10.1.3.2. Reviewer - Reviewing Activities

- Jean Clairambault, reviewer for different journals in 2018: PLoS Computational Biology, PLoS One, Integrative Biology, Applied Mathematical Modelling, Letters in Biomathematics, Journal of Theoretical Biology, Bulletin of Mathematical Biology, Mathematical Biosciences and Engineering
- Pierre-Alexandre Bliman, reviewer for the journals Automatica, Proceedings of the Royal Society of Edinburgh, Systems and Control Letters
- Diane Peurichard: reviewer for Journal of the Royal Society Interface, Processes, Computation
- Marie Doumic, reviewer for J. Math. Biol., SIAM App. Math., Ann. IHP, M2AN, Inverse Problems

10.1.4. Invited Talks

- Jean Clairambault: Workshop "Computational Systems Biology for Cancer", Paris, January 2018; Spring school "Mathematical Modelling of Tumour Growth and Therapy", CRM, Bellaterra (UAB, Barcelona), April 2018; Workshop "Modelling Biological Phenomena from Nano to Macro Scales", The Fields Institute, Toronto, May 2018; 4th Annual workshop on mathematics in medicine: mathematical models in cancer, Wolfgang Pauli Institut, Vienna, July 2018; Seminar, DIMEAS, Politecnico di Torino, October 2018; Mathematical and Computational Biology Workshop, Tirana, October 2018; International Conference on Applied Mathematics, Fes (Morocco), October 2018 ; Seminar on mathematical modelling of tissue growth, Les Treilles (Tourtour, France), November 2018; Workshop on Mathematical Challenges in the Analysis of Continuum Models for Cancer Growth, Evolution and Therapy, CMO, Oaxaca, November 2018 (see above: organisation of scientific events); International Program in Mathematical Biology Sep.-Dec. 2018, Institut Mittag-Leffler (Stockholm), December 2018
- Diane Peurichard: Oct 16-18 PSU-P6 workshop "Mathematics of living matter", Penn State; Jul 23-Jul 27 11th ECMTB Conference, Lisbon, Portugal; Apr 30 May 04 Workshop "Collective dynamics and self-organization in biological sciences", Edinburgh, Scotland.
- Marie Doumic: Keynote speaker at the BIOMATH 2018 conference, Sofia, Bulgaria, June 25-29 2018; 3h Minicourse for the Doctoral School of Vienna, Weissensee, July 2-5; Workshop "Collective dynamics and self-organisation in biological sciences", Edinburgh, April 30-May 4
- Dirk Drasdo: Paris, France, Sanofi, 7/11, Seminar: Spatial-temporal MultiScale-multilevel modeling OF DRUG-INDUCED LIVER DAMAGE and ITS Regeneration : Steps towards a VIRTUAL Liver; Paris, France, Ecopa, 6/11, Symposium: how new experimental tools in life science challenge the 3R vision. (5/6.11): Spatial-temporal MultiScale-multilevel modeling of APAP damage and its consequence on ammonia detoxification : Steps towards a virtual Liver; Palaiseau, France, Ecole Polytechnique, 19/10, Guess lecture. Integrated and spatial-temporal multiscale modeling of liver guide in vivo experiments in healthy & chronic disease states: a blue print for systems medicine?; Rome, Italy, 10/10, Mathematics for Biomedicine, 8-11/10: Integrated and spatial-temporal multiscale modeling of liver guide in vivo experiments in healthy & chronic disease states: a blue print for systems medicine?; Pisa, Italy, 5/10, Multiscale modeling and simulations to bridge molecular and cellular scales, 1-5/10: Multi-scale and integrated mathematical modeling of liver function and regeneration: Using mathematical models to guide experiments; Heidelberg, Germany, 1/11, BIOMS-Symposium 2018, 1-2/11: Multi-scale and integrated mathematical modeling of liver function and regeneration: Using mathematical models to guide experiments; Inst. Pasteur, France 20/9, Inst. Seminar: From systems biology to systems medicine: an example: Paracetamol overdose-caused damage & its regeneration: Virtual experiments in organ micro-architectures; Paris, France, 14/4, EASL, 11-14/4: Parameterization of liver metabolism; Lyon, France : From systems biology to systems medicine: an example: Paracetamol overdose-caused damage & its regeneration: Virtual experiments in organ micro-architectures

10.1.5. Leadership within the Scientific Community

Dirk Drasdo is member of the scientific leadership board of the German flagship project LiSyM (Liver Systems Medicine) financed by BMBF (Germany)

10.1.6. Scientific Expertise

- Jean Clairambault and Dirk Drasdo: members of the ANR CES 45 (mathematics and digital sciences for health and biology) selection committee
- Jean Clairambault: member of the review committee for the German FZJ (ForschungsZentrum Jülich)-BMBF funding measure "Demonstrators for Individualised Medicine" within the Framework of the Research and Funding Concept "e:Med Ð Paving the Way for Systems Medicine", Frankfurt, September 2018
- Jean Clairambault: member of the review committee for the German DLR (Deutsches Zentrum für Luft und Raumfahrt)-BMBF initiative "Systems medicine research consortia", Berlin, November 2018
- Jean Clairambault: representative of Inria (until June 2018) to the expert group of the ITMO Cancer (Aviesan) and member of the steering committee of the HTE program (2016-2020)
- Diane Peurichard and Marie Doumic: Ambassadeur FSMP for Austria
- Diane Peurichard: member of the selection committee Sorbonne Université, maitre de conference position
- Diane Peurichard: member of the Inria scientific selection committee (CORDI-S PhD, post-docs, delegation)
- Benoît Perthame has been member of the "Chern Prize" committee awarded at ICM 2018 in Rio.

10.1.7. Research Administration

- Pierre-Alexandre Bliman: Coordinator of the ECOS-Nord project C17M01 "News methods for controle of dengue and arboviroses epidemics".
- Marie Doumic: nominated in Dec. 2018 at the Scientific Council of INSMI, CNRS.
- Dirk Drasdo is member of the scientific leadership board of the German flagship project LiSyM (Liver Systems Medicine) financed by BMBF (Germany).
- Dirk Drasdo guides a research group bi-localized at Inria de Paris and IfADo, Dortmund, currently composed of 3 research engineers, 3 postdocs.

10.2. Teaching - Supervision - Juries

10.2.1. Teaching

Master : Philippe Robert, "Large Stochastic Networks", 24h, M2, Sorbonne Université, France.

Master: Marie Doumic, "Inverse problems in Biological Dynamics", 24h, M2, Sorbonne Université, France

Jean Clairambault: teaching in Spring school "Mathematical Modelling of Tumour Growth and Therapy" (4 one-hour lectures), UAB, Barcelona, April 2018 (see above); Fall teaching (3 one-hour lectures), Politecnico di Torino, October 2018 (see above)

Licence : Pierre-Alexandre Bliman, "Calculus 3", 90h, L2 and "Analyse", 60h, L3, Fundação Getulio Vargas, Rio de Janeiro, Brazil

Master : Diane Peurichard, "Fondements des méthodes numériques", 20h, "Calcul matriciel numérique" 20h

Licence : Diane Peurichard, Licence: "Introduction to Python" 20h

Master : Dirk Drasdo, "Agent-based models of tissue organization", UPMC M2 course, Paris **24 h / yr**

10.2.2. *Supervision*

PhD : Wen Sun, "A study of interacting stochastic networks : large scale, long time behavior and fluctuations", Sorbonne Université, June, 11, 2018, Philippe Robert

PhD : Veronica Quintuna Rodriguez, "New Network / IT Command: Virtualized Function Performance for a Programmable Infrastructure", Sorbonne Université, October 3, 2018, Fabric Guillemin and Philippe Robert.

PhD in progress : Gaëtan Vignoud, "Plasticity of Stochastic Neural Networks", September 1st, 2018, Philippe Robert, Laurent Venance

Jean Clairambault: supervision of the M2 ('mathematics of modelling') internship of Loïs Naudin: "Modélisation du métabolisme énergétique tumoral glycolytique vs. respiratoire oxydatif" and of two groups of four students of the L3 unit 3M101: "Excitabilité cellulaire : une première approche des systèmes dynamiques" and "Étude des équations de Lotka-Volterra"

Jean Clairambault: Supervision of PhD students Camille Pouchol (with Michèle Sabbah and Emmanuel Trélat, ED 386, Sorbonne Univerité, thesis defence June 2018: "Analysis, control and optimisation of PDEs, application to the biology and therapy of cancer" [1] and Ghassen Haddad (ED 386, Sorbonne Université, and Université Tunis-El Manar, co-supervisor: Slimane Ben Miled), thesis defence planned in December 2018: "Optimisation du traitement du cancer")

Internship: Supervision of Valeria Caliaro, M1 student from University of Verona (3months internship) on interacting particle networks, Diane Peurichard

Internship: Supervision of S. Zhenyu, M1 student from LJLL, Sorbonne University (3months internship) on coarse graining of a fluid filled with obstacles, Diane Peurichard

Diane Peurichard, Luis Almeida, Benoit Perthame: supervision of project CEMRACS (6weeks)

PhD defended: Noémie Boissier PhD defence in June 2018, supervision by D. Drasdo and I. Vignon-Clementel

PhD in progress: Adrian Friebel, "Software of image processing and analysis of liver tissue at histological scales", supervision by D. Drasdo and S. Hoehme

Internship: Ismael Gonzalez Valverde,PhD student from Zaragoza by Paul Van Liedekerke and Dirk Drasdo.

10.2.3. *Juries*

- Ph.D thesis of C. Pouchol, defended on June 29th: participation in the committee of J. Clairambault and B. Perthame.
- Ph.D thesis of M. Strugarek, defended on September 7th: participation in the committee of M. Doumic and B. Perthame.
- Dirk Drasdo was in 2018 member of the ANR-grant selection committee for mathematical modeling in medicine and biology.

10.3. Popularization

10.3.1. *Interventions*

- Marie Doumic: participation in a round table on December 13th, in Forum Emploi Maths, La Villette, Paris; Participation in a round table on "Science Meets Medicine", May 29th, in Vienna; presentation to a 12-year old class of pupils of mathematics for biology.
- Several Mamba members have taken part to the activities of the year of mathematical biology declared by European Mathematical Society.

- Dirk Drasdo on liver research and EASL: https://www.inria.fr/centre/paris/actualites/dirk-drasdo-et-ses-recherches-sur-le-foie

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[2] V. K. QUINTUNA RODRIGUEZ. *New Network / IT Command: Virtualized Function Performance for a Programmable Infrastructure*, Sorbonne Université, October 2018, https://hal.inria.fr/tel-01884431

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